REMARKS

Reconsideration of this application is respectfully requested.

I. Status of the Claims

Claims 55-57, 59-77, and 79-97 are pending in the application.

Claims 90-96 have been amended and no new matter has been added. Support for the amended claims can be found in the specification, for example, at page 7, line 15 to page 8, line 3; and page 21, line 1 to page 22, line 9. New claim 97 has been added and contains no new matter. Support for this new claim can be found in the specification, for example, at page 13, line 3 to page 16, line 2.

II. Information Disclosure Statement

The Examiner has stated that the Information Disclosure Statement (IDS) filed February 28, 2001 is improper because the citations are allegedly incomplete. Specifically, the Examiner has requested that the US Patents list the date, name, class and subclass, and that information for the foreign patents and publications be completed. The Examiner has acknowledged that the abstract of citation number 4 of the PTO Form 1449 filed with the IDS on February 28, 2001, DE 19501032 A1, has been considered.

This Amendment is accompanied by PTO form SB-08A in which each of the citations that had been listed in the February 28, 2001 PTO Form 1449 are listed in complete form. As requested by the Examiner, all information has been supplied for these citations. The Form SB-08A submitted herewith does not list any references not previously made of record in the February 28, 2001 PTO Form 1449.

It is respectfully noted that each of the references cited in the Form SB-08A submitted herewith was cited in an IDS and considered by the Examiner in the parent application U.S.S.N. 08/994,689. MPEP § 609(I)(A)(2) requires that the Examiner consider all information

which had been considered by the Office in a parent application. Thus, this Form SB-08A and the English abstract of DE 19501032 A1 are being submitted herewith solely in order to assure that these citations will be printed on the face of the patent that issues from the present application.

It is believed that the Applicants' duty to disclose information material to patentability under 37 § C.F.R. 1.56 has been met. Applicants respectfully request entry of the accompanying PTO Form SB-08 and withdrawal of the objection to the Information Disclosure Statement.

III. Objection to Claim 90

The Examiner has objected to claim 90, stating that the phrase "non-human transgenic mammal" should be amended to recite "transgenic non-human mammal." Claim 90 has been amended accordingly, and Applicants respectfully submit that the Examiner's objection is obviated and should be withdrawn.

IV. Rejections under 35 U.S.C. § 112, first paragraph- written description

Claims 55-57, 59-77, and 79-96 have been rejected for alleged failure to fulfill the written description requirement because of the phrase "joint-specific promoter." In this rejection, the Examiner states that (1) "... the specification and the art do not teach (sic, that) the Type II collagen promoter causes expression greater in joints than other tissues or causes expression in non-joint tissues is (sic) less than 10%"; and (2) "... one species in the genus is not adequate written description of that genus." Applicants traverse both grounds for rejection. As shown in the examples, the Type II collagen promoter is highly specific for the joints, and, in the context of the invention, the presence of one working embodiment that exemplifies the generic written description found in the specification constitutes an adequate written description of the claimed invention.

At the outset, Applicants note that the claimed invention is a specific type of transgenic animal. The Examiner has not argued that there is an inadequate written description of the claimed invention as a whole. Instead, the Examiner focuses on one element of the invention, a

tissue-specific promoter, and generates a rejection of the claims based on the supposed lack of written description of that single element.

The specification sets forth a generic written description of the claimed transgenic animal, of which joint-specific regulated expression is an important component. This one component of the invention, which, in context of the invention, operates like a specific part of a machine to achieve an animal as claimed. Applicants have more than adequately satisfied the written description requirement by providing an explicit description in words of this generic invention, and through examples of the invention's ability to degrade collagen in both spatial (joint) and temporal (inducible) regulation in an animal. ("Coordinated spatial and temporal control of MDE expression is preferably achieved by (i) placing expression of the repressor-activator fusion polypeptide or the transcriptional activator polypeptide under the control of a joint-specific promoter; (ii) placing the expression of the MDE or a derivative thereof under the control of a promoter responsive to the repressor-activator fusion polypeptide or the transcriptional activator polypeptide; and (iii) maintaining the transgenic animal during fetal development and early life under conditions in which MDE expression is repressed." See page 16, lines 7-13).

That said, even focusing on this element, which merely has a functional role in the transgenic animal invention, the Examiner's basis for this rejection is flawed. The specification fully describes joint-specific promoters in explicit language. See page 15, line 19 - page 16, line 9 ("Spatial control of MDE expression is achieved by the use of transcriptional promoters that direct transcription selectively in joint tissues. Joint-specific expression as used herein refers to expression that is greater in joints than in other cells; typically, the level of expression in non-joint tissues is less than 10% of the level of expression in joints. Preferably, expression in non-joint tissues is undetectable."); see page 6, lines 15-20 ("[T]he second recombinant gene is under the control of… a joint-specific promoter… most preferably, a type II collagen promoter… [resulting] in regulated joint-specific expression of the recombinant MDE"); page 36, line 21 - page 37, line 1 (describing "a gene encoding a tTA repressor-activator fusion protein operably linked to a joint-specific (type II collagen) promoter as well as a reporter gene suitable for assessing the tissue-specific expression conferred by the type II collagen promoter."); and Examples 4 and 5 of the specification. The specification clearly teaches that spatial control of MDE expression is achieved

by the use of transcriptional promoters that direct transcription selectively in joint tissues. (See specification at page 15, lines 19-20). Such joint specific expression, for example, produces expression in non-joint tissue of less than 10% compared to the joints, and preferably not at all. (Ibid. at lines 20-23). One source of such joint specific promoter sequences includes those derived from the collagen Type II promoter. (See specification at page 16, lines 1-2). In contrast to the Examiner's assertion, the examples show that expression under control of this promoter is spatially limited to the joints. (See specification at page 40, lines 1-22). Additionally, the specification teaches that such joint-specific promoter sequences may comprise one or more copies of particular sequences or sub-sequences, and that these may be in direct or inverted orientation relative to each other or the sequence being regulated. (Ibid. at lines 2-6). Clearly, Applicants have not only defined the term "joint-specific promoters," but have also taught how these sequences are to be arranged and provided examples of where the sequences can be derived from.

The concept of joint-specific promoters was well-known in the art at the time of invention. As set forth in the Second Neuhold Declaration (paragraph 7; a copy of the Second Neuhold Declaration and its accompanying Exhibits (Tabs 1-9), which were originally filed in the parent case U.S.S.N. 08/994,689 on August 31, 2000, was filed as Exhibit 5 with the April 30, 2002 Amendment and Response in the instant application), the specific promoter employed to achieve tissue specific expression does not make any difference, as one of ordinary skill in the art would readily appreciate. A number of issued patents that cover transgenic animals establish that claims reciting generic tissue-specific expression of a transgene do not offend the written description requirement, because the actual tissue specific promoter is usually of no moment. See for example U.S. Patent Nos. 5,625,124 (claim 1: "gut epithelial cell specific promoter"); 5,880,327 (claim 1: "a mammary-gland specific promoter"); 5,917,123 (claim 1: "a cardiac-specific regulatory region"); and 6,028,245 (claim 1: "a promoter that drives expression of the transgene in skin") (all attached as Exhibit 8 with the April 30, 2002 Amendment and Response in the instant application).

The Examiner asserts that "[w]hat is required is a description of a reasonable number of promoters having that function." (Office Action, p. 3, second paragraph). However, a representative number of examples serves as an adequate written description of a genus in the absence of an express description of the genus. See *Regents of the University of California v. Eli*

Lilly, 119 F.3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) ("A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus *or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*") (emphasis added). Thus, either representative examples <u>or</u> a generic description of structural features common to the genus constitute an adequate written description of a genus.

In the present invention, the generic description is a mammal, which is a structurally identifiable genus, in which a regulator of gene transcription is under expression control of a tissue-specific promoter. The structure of the genetic elements includes the relative position of the promoter to the regulator of gene transcription and the nature of both as parts of DNA molecules. This combination of structure (transgenic mammal with specified modifications to its genome) and function (joint-specific promoter) sets forth the common members of the genus in a way that distinguishes them from other transgenic mammals, and demonstrates possession in the inventor's mind (conception) of the claimed invention. The broad concept corresponds directly to the exemplified species.

The specification clearly describes joint-specific promoters capable of use in a transgenic animal of the invention. More importantly, the specification sets forth in detail a written description of how this element relates to the other elements of the invention, to provide a sufficient disclosure that "... allow[s] one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Enzo Biochem, Inc v. Gen-Probe Inc.*, 296 F.3d 1316, 1329, 63 USPQ2d 1609, 1616 (Fed. Cir. 2002). Whether one practices the invention with a Type II wildtype collagen promoter, such a promoter with rearranged orientation, or some other perhaps as yet undisclosed promoter that provides for joint-specific expression, e.g., the level of expression in other tissues is no more than 10% of the level of expression in the joint, makes no difference as to <u>the claimed invention</u>. Accordingly, it is believed that this rejection of the term "joint-specific promoter" has been obviated and Applicants respectfully request its withdrawal.

V. <u>Rejections under 35 U.S.C. § 112, first paragraph- enablement</u>

Claims 54-57, 59-77, and 79-96 have been rejected for alleged failure to fulfill the enablement requirement because the specification allegedly does not enable any transgenic non-human mammal, or any joint-specific promoter. The Examiner alleges that at the time of filing, the specification was not enabling for non-human transgenic animals because expression of MMP in the joints of an animal would not predictably produce cartilage degradation. The Examiner argues that the state of the art demonstrated that closely related species carrying the same transgene construct can display widely varying phenotypes. The Examiner has failed to recognize that, at the time of invention, it was well known in the art that, as set forth in the specification: (1) both matrix metalloproteinases (MMPs) and Type II collagen are highly conserved between species; (2) MMPs as recited in the claims degrade Type II collagen; (3) degradation of Type II collagen results in cartilage damage; and (4) generation of transgenic animals was routine. Based upon the highly conserved nature of MMPs and Type II collagen, the known link between Type II collagen degradation and cartilage damage, and the routine nature of generating transgenic animals, it would have been predictable that expression of an MMP in the joints of different species would result in the same phenotype, i.e., cartilage degradation.

MMPs Are Highly Conserved Across Species

First, at the time of invention, MMPs were known to be highly conserved across species, and their ability to degrade Type II collagen was well known. See page 11, lines 14-21 ("Any polypeptide exhibiting matrix-degrading activity may be used in practicing the invention.... The enzymes may be derived from any animal species"; see also J. Freije, J. Biol. Chem., 269(24):16766-73, 16767 (June 1994) ("Freije") (Exhibit A); R. Billinghurst, J. Clin. Invest, 99(7):1534-1545, 1534 (April 1997) ("Billinghurst") (Exhibit B). Freije discloses that as early as 1988, it was known that MMPs showed highly conserved sequence motifs. Freije at 16768. These sequence motifs are highly conserved between mammalian species, and are largely responsible for MMP activity. *Id.*; see also S. Matsumoto, Biochim. Biophys. Acta., 1307(2):137-139 (June 1996) ("Matsumoto") (abstract only) (Exhibit C); P. Mitchell, J. Clin. Invest., 97(3):761-768, 761 (Feb. 1996) ("Mitchell") (Exhibit D). Mitchell characterizes MMPs broadly as "vertebrate collagenases,"

and further discloses that MMPs were known to possess similar activity and function between species. Mitchell at page 761 (homologous rat and human MMPs show similar turnover rate and substrate affinity). Thus, it would be predictable that MMPs expressed in different species, sharing the same or similar highly conserved sequence motifs, would display the same function and activity, and thus would cleave Type II collagen.

Type II Collagen Is Highly Conserved Across Species

Second, it was well known in the art that Type II collagen is also highly conserved between species. Type II collagen is well known to be found in all multicellular organisms, sharing common structure and properties, and being the form of collagen found in cartilage. See Stryer, Biochemistry, 2d Ed., 185-197, 185 (1975) (Exhibit E). Type II collagen comprises 90-95% of mammalian articular cartilage, forming fibrils that provide tensile strength and maintain integrity. Billinghurst at 1534 (Exhibit B). The structure of Type II collagen was known to be "extremely well conserved." M. Vikkula, FEBS Lett. 3; 250(2):171-174 (Jul. 1989) (abstract only) (Exhibit F); P. Wooley, Crit. Rev. Immunol. 8(1):1-22 (1987) (abstract only) (Exhibit G). Type II collagen was known to be greater than 80% conserved between mice, rats, chickens, cows, and humans. K. Cheah, Mamm. Genome, 1(3):171-183 (1991) (abstract only) (Exhibit H). Coupled with the well known conservation of MMP sequence and function, it would be predictable that Type II collagen-specific MMPs would degrade Type II collagen among many different species, since Type II collagen structure is also highly conserved. Thus, contrary to the Examiner's assertions, a species-specific requirement is not necessary, since it would be predictable and expected that MMPs would degrade Type II collagen, regardless of species.

Degradation Of Type II Collagen Results In Cartilage Damage

Third, it was known in the art that degradation of Type II collagen resulted in cartilage damage. Billinghurst discloses that damage to Type II collagen is a critical event in the development of arthritic conditions. Billinghurst at 1534 (Exhibit B). Cartilage damage and degradation is a well known characteristic of osteoarthritis, and is known to afflict many vertebrates. A. Hough, Pathology of Osteoarthritis, in Arthritis and Allied Conditions, vol. 2, 1699-1707 (1993) (Exhibit I). Expression of phenotypes associated with cartilage damage is clearly

supported in the specification. See page 18, lines 14-19; page 19, lines 17-23; page 21, lines 4-6. Thus, based upon the state of the art and the disclosure of the present invention, it would have been predictable that degradation of Type II collagen would result in cartilage damage.

The references cited by the Examiner allegedly contradict the teaching of the specification. However, the present invention involves expression of enzyme transgenes and degradation of Type II collagen with a high level of sequence, structural, and functional conservation. The Examiner has failed to provide any evidence that the transgenes utilized in the references cited (Ren-2 in Mullins 1990 and Mullins 1989; HLA-B27 in Hammer 1990 and Taurog 1988) have any predictive value of the claimed transgenic mammals that express MMPs. Thus, these references are not indicative of non-enablement of the present invention.

Generation Of Transgenic Animals Is Routine, And Their Phenotype Predictable

Lastly, generation of a transgenic animal is routine, and adequately supported by the specification. See page 22, line 15 to page 26, line 8; page 17, line 21 to page 18, line 6. The specification clearly outlines and enables methods for generating particular nucleotide constructs and transforming animals with such constructs. See page 33, line 1 to page 39, line 20. Practicing the disclosed techniques was routine for one skilled in the art, because "... contrary to the examiner's assertions, as of 1996 creation of transgenic mammals required no more than ordinary technical efforts – indeed, technical efforts with shortcomings that are readily overcome." Neuhold Declaration, paragraph 9. This clear assertion by one of ordinary skill in the art must carry greater weight than the Examiner's characterizations of the cited transgenic animal references. Based upon the disclosure in the specification, generating transgenic animals with similar constructs would be a routine matter for one skilled in the art. Once the transgenic animals are generated, it is a routine matter to screen the animals for expression of the transgene and degradation of collagen.

Once a transgenic animal was generated, and the MMP expressed, it would be a matter of course that cartilage degradation would occur. As discussed above, the high level of sequence conservation in both MMPs and Type II collagen would predictably result in collagen degradation in the transgenic animal, leading to cartilage degradation. Thus, expression of MMPs in the joints of any non-human transgenic animal would predictably produce cartilage degradation,

and result in the phenotype of the present invention. Thus, given the disclosure of the specification and the state of the art at the time of invention, a person skilled in the art would have predicted the phenotype generated by expression of MMPs in the joints of a non-human transgenic animal.

The References Cited By The Examiner Support Enablement

The Examiner also cited references previously of record, namely Cameron (1997), Mullins (1990), Hammer (1990), Mullins (1989), Taurog (1988), Mullins (1996), Mullins (1993), Ebert (1988), Wall (1996), and Overbeek (1994) to support the rejection over the alleged lack of enablement of a transgenic mammal. As explained in prior amendments, the references cited by the Examiner merely demonstrate that which the skilled artisan in the field of transgenic mammals knows as well as his comrade who generates monoclonal antibodies from hybridomas (or phage display for that matter), or the one who clones individual genes from libraries of cDNAs created from cells or tissues of interest: like most of biology, the process is empirical and involves substantial trial and error, but ultimately, with the proper selection and screening criteria, yields a few successes. In this respect, the process falls well within the parameters set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) (enablement of broad monoclonal antibody claims despite the larger number of trials necessary to obtain the operative antibody).

Viewed properly, all of the references cited by the Examiner support enablement, because they establish that creating transgenic animals involves routine manipulations and multiple trials to find individuals with the desired genotype and phenotype. As discussed above, inserting the transgene of the present invention into different species of animal would result in the same phenotype, due to the conservation of both MDEs and Type II collagen. In addition to selecting animals with the proper genotype, which the Examiner does not suggest is not enabled, the specification also sets forth routine screens for the desired phenotype. See page 18, line 22 - page 19, line 2; see also Examples 4-6, page 40, line 1 - page 45, line 7. The conservation of MDEs and Type II collagen, combined with the routine manipulations disclosed by the references cited by the Examiner, establishes that it would be routine and predictable for a person skilled in the art to generate a transgenic animal with the desired phenotype of the present invention.

Cameron discusses the effects of the placement of the transgene with respect to the overall chromatin structure on transgene expression. Nothing in Cameron correlates diversity of chromatin structure with species-specificity. Cameron's description of the effect of placement of the transgene with respect to overall chromatin structure is a relevant issue even within species and is not species dependent. (See p. 256, col. 2, lines 3-9 of Cameron). Cameron describes that such effects are seen with transgenic mice (not between species) made with the same construct. Thus, Cameron supports Applicants' assertion that at the time of the present invention, it was routine for one skilled in the art to screen, whether screening be done within or between species, for transgenic animals that work, i.e., in which transgene insertion occurs at an accessible location in the chromosome. In other words, the requirement to screen and select for a desired transgenic animal is wholly independent of the species selected. Cameron does not correlate genetic diversity or species diversity with unpredictability of transgene expression. Rather, Cameron discloses that all transgene expression depends on random insertion of the transgene in a productive integration site, both within and between species, and that it is routine for one skilled in the art to test and make multiple transgenic animals to find one with the desired phenotype.

In the present Action, the Examiner has cited Mullins (1993) for teaching that integration of a transgene into a different species of animal results in divergent phenotypes. Mullins (1993) is simply a review article that summarizes references that were already of record (specifically Mullins (1990) and Hammer (1990) (see p. 631, Col. 1, end of ¶ 1 of Mullins (1993)). These references also show that, as with many experimental biological processes, creating a desired transgenic animal requires multiple trials with screening and selection processes to select the successes. The Examiner has failed to establish any reason why the creation of transgenic animals differs from the other biological arts, such as that discussed in *In re Wands*, in this respect.

Mullins (1989) reports success in generating transgenic mice to study tissue-specific expression and control of the Ren-2 gene. Mullins states that expression of the transgene can vary depending on many factors, including the site of integration and the copy number integrated (page 4070). The article shows that even among successfully generated transgenic mice, there is variability in the level of expression. Applicant submits that the potential variability is irrelevant, and that the variable levels of success, or even failure, is a routine part of the generation of

transgenic mammals. Indeed, as reported in Example 5 and the First Neuhold Declaration at para. 8, applicants observed variability in expression in the exemplified founder mice.

Taurog (1988) reports success introducing the MHC Class I antigen HLA-B27 into both inbred and hybrid mice, for use in studying the role of HLA-B27 in inflammatory human disease. In order to generate the transgenic mice, over 600 embryos were fertilized, with less than 1/6 of these embryos generating live pups (see page 4021-4022). An even smaller fraction expressed HLA-B27 in significant amounts (see Id.). Applicant submits this reference shows that although the number of failures is large, it is routine for such failures to occur, and that the failures are irrelevant in light of the eventual success. Nothing in Taurog suggests that screening and selecting of the successes required other than routine experimentation.

Mullins (1996) reports that transgenic technology, including embryonal stem (ES) technology, was well established at the time of invention (page S37). Time and cost, issues irrelevant to enablement, limit the desirability of pronuclear injection in larger mammals. Mullins 1996 at page S37. No matter, as pointed out in the specification, ES technology is an alternative. See page 25, line 1 - page 26, line 8. Pronuclear injection also provides for transgene insertion. See page 23, line 13 - page 24, line 3. The fact that pronuclear injection is less efficient, and therefore economically undesirable, does not establish that it does not work. On the contrary, nothing in Mullins (1996) supports such a conclusion. In any event, this paper reports a number of successful non-murine transgenic animal models (see page S38).

Ebert (1988) reports success generating experimental transgenic animals for disease models ("Transgenic pigs carrying this fusion gene had elevated levels of circulating human somatotropin"; see page 277). Applicants submit that the presence of failures is irrelevant in the face of success; the entire history of modern molecular and cellular biology is one of selecting and screening for successes from the much more abundant failures, as demonstrated in *In re Wands*.

Wall reports that 6000 papers describe transgenic animals, mostly mice, to answer research questions (pages 58, 60, and 61). Wall states that "genes can… be modified to function very differently than they do in their native form (gene products, tissue specificity, and timing of expression can be altered)" (page 58). In other words, Wall specifically states that the features of

Applicants' invention can be achieved. Wall does concede that transgenic farm animals are costly (mostly because it takes many attempts to yield the desired transgenic animal) (see page 6), however, economic issues are irrelevant to enablement. How is it possible that a reference acknowledging such an abundance of research papers on transgenic animals, manipulation of expression, and at least 1% efficiency of obtaining the desired transgenic animal (much higher, one might add, than the likelihood of obtaining a desired monoclonal antibody or even cloning a gene) calls into question enablement of this invention? On the contrary, Applicants submit such a reference supports the routine nature of generating experimental transgenic animals for disease models.

Overbeek shows that different transgenic animals within a single species will demonstrate different levels of expression. Regulatory sequences help avoid variability (see page 97) but this makes little difference: variability ranges from one extreme to another, from no phenotypic change to the desired change. This establishes predictability of two things: there will be failures, and there will also be successes. By selecting the successes, which is routine, one obtains the desired transgenic animals. Indeed, applicants themselves had failures, however, successful animals were obtained (see specification at page 43).

For these reasons, and the reasons previously made of record, none of the references cited by the Examiner establish lack of enablement with respect to the claimed "transgenic non-human mammals." Such animals are enabled; given the tools (in this case the MDE, regulated expression system, and tissue-specific expression system) and the mechanisms for testing (any of the indicia of collagen II degradation), it is merely routine experimentation to make and test transgenic animals to find one that works. As pointed out above, making a transgenic animal involves the same empirical testing process as making any other biotechnological material. In *In re Wands* the courts have acknowledged that in the field of biology, a lot of experimentation can be necessary and that most attempts to achieve the experimental goal will result in failure, but that as long as one can screen for successful results, such experimentation does not constitute undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. For example, in *In re Wands*, the court found the following process did not constitute undue experimentation:

by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest. 858 F.2d at 738

The Examiner has not addressed Applicant's contention that the references cited by the Examiner to support lack of enablement establish the opposite proposition: each of these references show that a useful transgenic animal was created through the empirical process that enables the claimed invention. These references also show that, as with many experimental biological processes, creating a desired transgenic animal requires multiple trials, with screening and selection processes to identify and select the successes. The Examiner has failed to establish any reason why creation of the transgenic animal differs from the other biological arts, such as that discussed in *In re Wands*.

The Examiner also alleges that several animal models of disease have relied on transgenic rats when the development of mouse models was not feasible, and argues that closely related species carrying the same transgene can exhibit widely varying phenotypes. The Examiner alleges that Mullins 1989 and Mullins 1990 show, respectively, the failure to generate a transgenic, hypertensive mouse expressing Ren-2, followed by successful generation of a transgenic, hypertensive rat. However, unlike the phenotype of the present invention, "the mechanism responsible for elevating blood pressure remains to be established." Mullin 1990 at page 543. Thus, other, unknown factors may be responsible for the generation of the hypertensive phenotype in rats, and may cause the difference in results observed in Mullins 1989 and Mullins 1990. In contrast, the mechanism for cartilage degradation in accordance with the claimed invention is known, e.g., Type II collagen degradation by MDEs. In combination with the fact that the elements of the mechanism of cartilage degradation are highly conserved, it is therefore possible to predict the phenotype of a transgenic animal expressing the transgene of the present invention. See page 11, lines 14-21, and Freije at 16767.

Similarly, the Examiner argues that Taurog 1988 and Hammer 1990 respectively show the failure to generate a HLA-B27 transgenic mouse with an inflammatory disease phenotype, followed by successful generation of a transgenic rat. However, the HLA-B27-associated disorders comprise a large group of heterogeneous disorders, and the common pathogenic mechanism

underlying these disorders is unknown. Thus, the unpredictable results observed in Taurog 1988 and Hammer 1990 are most likely due to the lack of knowledge regarding the underlying disease mechanisms. These references cannot be used to establish unpredictability of the phenotype of the present invention, because the pathogenic mechanism for cartilage degradation in the invention is known and the elements of the mechanism are highly conserved. See page 11, lines 14-21, and Freije at 16767. Therefore the phenotype of a transgenic animal of the present invention is predictable.

Finally, the Examiner cites references from almost a decade before the application filing date, namely, Mullins (1990), Hammer (1990), Mullins (1989), Taurog (1988), Mullins (1993), and Ebert (1988). Such dated references cannot constitute the state of the art, because "[e]nablement is determined from the viewpoint of persons of skill in the field of the invention at *the time the patent application was filed.*" *Ajinomoto Co., Inc. v. Archer DanielsMidland Co.*, 228 F.3d 1338, 1345, 56 USPQ2d 1332, 1337 (Fed. Cir. 2000) (emphasis added). To establish the viewpoint of persons of skill in the field on the basis of references over ten years prior to the time the application was filed ignores technical advances that occur between the time the reference was published and the time the application was filed. A difference of over ten years is enough that "in view of the rapid advances in science... what may be unpredictable at one point in time may become predictable at a later time." *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374, footnote 10, 52 USPQ2d 1129, 1138, footnote 10 (Fed. Cir. 1999).

The Joint-Specific Promoter Is Enabled In View Of The Invention As A Whole

With respect to the joint-specific promoter, the disclosure and examples show that one can practice the claimed invention (a transgenic mammal capable of degrading collagen primarily or exclusively in the joints of a temporally controlled fashion) using any joint-specific promoter. As outlined above, in the discussion of the rejection under 35 U.S.C. § 112, first paragraph – written description, there is literal support in the specification for joint-specific promoters. In the context of the entire invention, expression of MDEs are necessarily joint-specific; otherwise, the transgenic mammals would suffer from non-specific, systemic degradation of collagen throughout the body. See page 4, line 14 - page 5, line 3 (constitutive expression of MDEs

causes embryonic lethality). Given the importance of tissue-specific expression of the transgene to the invention and the ease with which one of ordinary skill can substitute one promoter for another, it is well within the level of skill for one in the art to use any joint-specific promoter in this invention, whether known or yet to be discovered, to limit expression of the MDEs to the transgenic animal's joints. As discussed above, the concept of tissue-specific promoters was well-known in the art at the time of invention. In other words, as disclosed in the application, tissue-specific expression is very important, but the exact tissue-specific promoter used to achieve it matters very little.

The specification adequately discloses a method for making and using the present invention; disclosing other methods by which the claimed invention may be made is not necessary. See *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987). Because joint-specific promoters were well known in the art at the time of invention, it is not required to specify other joint-specific promoters that may be used in the method disclosed in the present invention. The joint-specific promoter is a single element in the claimed method, and given that joint-specific promoters are well known in the art, cannot be viewed in isolation to justify an enablement rejection.

Furthermore, Applicants are not required to enable any joint-specific promoters that arise *after* the date of filing. The Court of Appeals for the Federal Circuit has recently stated that the "law does not expect an applicant to disclose knowledge invented or developed after the filing date." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) (holding that, despite the lack of specific reference to chimeric antibodies in the specification, the enablement requirement was satisfied with regard to chimeric antibodies because chimeric antibody technology did not arise until after the application was filed). Technology arising after the filing date is "by definition, outside the bounds of the enablement requirement," and is enabled by the specification provided that the generic description in the specification encompasses the new technology. *Id.* Applicants have met their burden of enabling the genus of joint-specific promoters by adequately enabling Type II collagen promoters, and the generic description is broad enough to cover any joint-specific promoters arising after the filing date. See page 15, line 19 - page 16, line

6. Thus, Applicants are not required to enable any joint-specific promoters identified after the application was filed.

In short, the Examiner's grounds for rejection are in error given the advanced state of the art, including general recognition of enablement of creation of transgenic animals (irrespective of whether or not such efforts are cost effective), widespread knowledge of regulatable expression systems, the understanding in the art of tissue-specific expression, and the number of well known extracellular matrix degrading enzymes from which to choose. The present invention is broadly enabled, and the Examiner has not met his burden of challenging enablement. Accordingly, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph is in error and respectfully request that the rejection be withdrawn.

VI. Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 90-96 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularity point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that the phrase "control transgenic mammal in which the composition was not administered by expression of the metalloproteinase was activated" is unclear, since it is unclear whether the control animal has the same genome as the animal of step (a), or whether the control animal has had MMP activated, collagen degradation, or one of the phenotypes listed in step (a). Claims 90-96 have been amended as per the Examiner's recommendations to more clearly recite the aforementioned elements.

The Examiner further stated that the phrase "phenotypic change" is inaccurate because the phenotype does not change, and that the phenotypes are compared to one another. Claims 90-96 have also been amended to recite that the test involves "comparing the phenotype of the first transgenic non-human mammal" or rat "to which the composition was administered with the phenotype of the second transgenic non-human mammal" or rat "in which the composition was not administered" in step (c).

In view of these amendments, Applicants respectfully submit that the Examiner's rejection is addressed and should be withdrawn.

CONCLUSION

In view of the foregoing, it is believed that claims 55-57, 59-77, and 79-97 are in condition for allowance and it is respectfully requested that the application be reconsidered and that all pending claims be allowed.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: August 9, 2004

Respectfully submitted,

By Heather Morehouse Ettinger Reg. No. 51,658 for Paul F. Fehlner

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